TABLE 62 Summary of quality assessment of Norum[60] using the critical appraisal checklist from Evers and colleagues[57]

Item		Yes/no
1	Is the study population clearly described?	Yes. Patients with metastatic colorectal cancer having received two lines of treatment
2	Are competing alternatives clearly described?	Yes. The comparator is no third-line therapy
3	Is a well-defined research question posed in answerable form?	Yes. The cost per LYG from changing policy from no third-line therapy to cetuximab plus irinotecan in the treatment of metastatic colorectal cancer
4	Is the economic study design appropriate to the stated objective?	Yes. A model-based cost-effectiveness analysis is used reporting cost per LYG
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported, but Norum states that 'All costs occurred within one year and were not discounted' (p. 533)
6	Is the actual perspective chosen appropriate?	Yes. The cost-effectiveness analysis is conducted from a third-party payer perspective in Norway
7	Are all important and relevant costs for each alternative identified?	Yes. Total costs include drug acquisition and administration, hospitalisation, outpatient therapy, EGFR analysis and family (travel) costs
8	Are all costs measured appropriately in physical units?	Yes. All costs were calculated according to Norwegian unit costs and converted to euros
9	Are costs valued appropriately?	Yes
10	Are all important and relevant outcomes for each alternative identified?	Yes. LYG is the outcome used
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined as LYG and is based on data in BOND[49] and Saltz *et al.*[40]
12	Are outcomes valued appropriately?	Yes
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, and subjected to sensitivity analyses
14	Are all future costs and outcomes discounted appropriately?	No. No discounting was applied
15	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	Yes. One-way sensitivity analyses on all health-care costs (EGFR analysis cost, cetuximab and irinotecan drug costs, outpatient clinic cost, drug administration cost) and treatment impact on overall survival. The impact of travelling costs was not assessed in sensitivity analyses
16	Do the conclusions follow from the data reported?	Yes. Third-line therapy with cetuximab plus irinotecan was acknowledged to be promising but very expensive. Lower drug costs and/or improved survival could change these findings. This conclusion reflects the high base-case ICERs reported and the lower ICERs from assuming reduced drug costs and improved survival
17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	To some extent. The author discusses differences in cost of cetuximab acquisition between countries and also the willingness-to-pay thresholds in different countries
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	The author acknowledges a research grant from the Norwegian Cancer Union for this work. There is no indication that this would represent a conflict of interest
19	Are ethical and distributional issues discussed appropriately?	No

TABLE 63 Summary of quality assessment of Starling and colleagues[61] using the critical appraisal checklist from Evers and colleagues[58]

Item		Yes/no
1	Is the study population clearly described?	Yes. Patients with metastatic colorectal cancer who have failed previous chemotherapy treatment
2	Are competing alternatives clearly described?	Yes. Active/best supportive care, where active supportive care is the best care available and may include chemotherapy
3	Is a well-defined research question posed in answerable form?	Yes. To compare the cost-effectiveness of cetuximab plus irinotecan with active/best supportive care
4	Is the economic study design appropriate to the stated objective?	Yes. A trial-based cost-effectiveness analysis of Cunningham *et al.*[49]
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes. A lifetime horizon extrapolating beyond the end of follow-up in Cunningham *et al.*[49]
6	Is the actual perspective chosen appropriate?	Yes. The study was calculated from a third-payer perspective: NHS
7	Are all important and relevant costs for each alternative identified?	Yes. Drug acquisition and administration, inpatient hospitalisation, outpatient consultations, laboratory tests (including EGFR testing) and imaging
8	Are all costs measured appropriately in physical units?	Yes
9	Are costs valued appropriately?	In pounds sterling, but source provided if unit costs not reported
10	Are all important and relevant outcomes for each alternative identified?	Yes. The primary health outcome is LYG with a secondary outcome of QALYs using utility values from the MABEL study
11	Are all outcomes measured appropriately?	Yes. EQ-5D utility values from the MABEL study
12	Are outcomes valued appropriately?	Unclear. Although utility values are reported to have been measured directly from Cunningham *et al.*,[49] the mean utility reported by MABEL 'was applied to all patients at all time points in the economic model' (p. 209)
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, and subject to sensitivity analyses
14	Are all future costs and outcomes discounted appropriately?	Unclear. Discounting is not reported
15	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	Yes. In one-way sensitivity analyses the following were assessed: proportion of active/best supportive care patients receiving chemotherapy, overall survival, cetuximab acquisition costs, chemotherapy administration costs and best supportive care costs
16	Do the conclusions follow from the data reported?	The conclusion does not reflect on any of the results reported
17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	Yes. The authors comment that use of one RCT for the basis of the cost-effectiveness analysis 'may lead to a partial and limited analyses to inform decision making' (p. 211)
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	The cost-effectiveness analysis was undertaken by the authors on behalf of Merck KGaA, Darmstadt. One author has received research funding from Merck and participated in advisory boards for Merck and Pfizer
19	Are ethical and distributional issues discussed appropriately?	No

TABLE 64 Summary of quality assessment of Annemans and colleagues[59] using the critical appraisal checklist from Evers and colleagues[57]

Item		Yes/no
1	Is the study population clearly described?	Yes. Patients from the BOND[49] study and patients receiving current care. Details on age, gender, body surface area and the number of previous chemotherapy regimes are reported
2	Are competing alternatives clearly described?	Yes. Current care received by patients in three major oncology centres, with 80% of patients receiving chemotherapy third line
3	Is a well-defined research question posed in answerable form?	Yes. Comparison of the cost-effectiveness in Belgium of cetuximab plus irinotecan and current care in EGFR-expressing metastatic colorectal cancer patients who have failed irinotecan-containing therapy
4	Is the economic study design appropriate to the stated objective?	Yes. Retrospective cost-effectiveness analysis based on BOND and a matched population of patients, reporting cost per LYG
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported
6	Is the actual perspective chosen appropriate?	Yes. From the perspective of the health-care system in Belgium
7	Are all important and relevant costs for each alternative identified?	Yes. Cetuximab and irinotecan acquisition costs and the cost of drugs for treating adverse events. Additional costs included were for laboratory tests, imaging, consultations, hospitalisations and any subsequent chemotherapy
8	Are all costs measured appropriately in physical units?	Yes. Costs are reported in euros. Resource use data were derived directly from patient records
9	Are costs valued appropriately?	Yes. Costs were derived from Belgian unit costs
10	Are all important and relevant outcomes for each alternative identified?	Yes. LYG is the outcome used
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined by overall survival based on data from the BOND study
12	Are outcomes valued appropriately?	Yes
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, with two scenarios presented as base-case analyses (6- and 12-week treatment continuation rule)
14	Are all future costs and outcomes discounted appropriately?	Unclear. Discounting is not reported
15	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?	Yes. The impact of changing survival and cost data in the current care arm is described
16	Do the conclusions follow from the data reported?	Yes. The conclusion states that cetuximab plus irinotecan is 'rather cost-effective in Belgium' (p. 424) and this reflects the ICERs reported of €17,000 and €40,000 per LYG, according to whether cetuximab was discontinued at 6 or 12 weeks if there was no tumour response at those times
17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	To some extent. The authors state that current care in the major oncology centres may not reflect that in smaller centres
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Unclear. There are no acknowledgements to a funding source. All authors are affiliated with either a university or a hospital
19	Are ethical and distributional issues discussed appropriately?	No

TABLE 65 Summary of quality assessment of Wong and colleagues[62] using the critical appraisal checklist from Evers and colleagues[57]

Item		Yes/no
1	Is the study population clearly described?	Yes. Hypothetical cohort of 1000 patients with newly diagnosed metastatic colorectal cancer. Patients supposedly received up to three lines of treatment before supportive care and death
2	Are competing alternatives clearly described?	Yes. In total, nine possible treatment strategies are modelled. Five of these involve cetuximab third line
3	Is a well-defined research question posed in answerable form?	Yes. To measure the cost implications of treatment with sequential regimens that include chemotherapy and/or monoclonal antibodies
4	Is the economic study design appropriate to the stated objective?	Yes. Model-based cost-effectiveness analysis reported as cost per discounted life-year
5	Is the chosen time horizon appropriate to include relevant costs and consequences?	Unclear. Time horizon is not reported
6	Is the actual perspective chosen appropriate?	Yes. Third-party payer
7	Are all important and relevant costs for each alternative identified?	No. Only costs related to drug acquisition and administration were modelled. Costs associated with supportive care medications, toxicity management, radiographic assessments or physician visits were not modelled
8	Are all costs measured appropriately in physical units?	Yes. Drug costs measured in US$ based on average patient weight of 75 kg and body surface area of 1.9 m^2
9	Are costs valued appropriately?	Yes. Drug costs are based on average sales prices
10	Are all important and relevant outcomes for each alternative identified?	Yes. Drug toxicity and discounted life-years
11	Are all outcomes measured appropriately?	Yes. Treatment benefit is defined by overall survival, and for cetuximab treatments it is based on data from Cunningham *et al.*[49]
12	Are outcomes valued appropriately?	Yes
13	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, and with a cost-effectiveness frontier presented
14	Are all future costs and outcomes discounted appropriately?	Yes. Life expectancy and costs are discounted at 3% per year
15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes. One-way sensitivity analyses were performed for changes in toxicity, progression, drug costs, time on supportive care and cost of supportive care
16	Do the conclusions follow from the data reported?	Yes. The authors report that the most effective regimens came at very high incremental costs, reflecting the large ICERs reported
17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	To some extent. The authors comment that changes in drug costs in the future will impact on the cost-effectiveness of these drugs
18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Conflicts of interest are declared. One author has received funding from Bristol-Myers Squibb while the other three authors have acted as consultants and/or received honoraria from Amgen, Genentech, Pfizer, Sanofi-Aventis, Roche and/or Bristol-Myers Squibb
19	Are ethical and distributional issues discussed appropriately?	No